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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/554,292

09/22/2006

Herve Porchet

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EXAMINER

BORGEEST, CHRISTINA M

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/554,292	Applicant(s) PORCHET ET AL.	
	Examiner Christina Borgeest	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/2005; 9/2006</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II (claims 9-17) in the reply filed on 15 January 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-8 and 18-25 are cancelled. Claims 9-17 are under examination.

Information Disclosure Statement

The information disclosure statement (IDS) filed 1 September 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it contains references that are duplicates of those on the IDS filed 26 October 2005, namely U.S. Patents: 5,240,584, 5,134,122, U.S. Patent publication 2002/0065260 and WO document WO94/26207. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The disclosure is objected to because of the following informalities. A Brief Description of the Figures heading is needed in the specification (see page 12). Furthermore, the Brief Description of the Figures should be moved to page 6 before the Detailed Description. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use:

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if

the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Finally, the title should be changed to reflect the invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 12, 13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Oettel et al., (U.S. Publication 2002/0065260, published 30 May 2002—on Applicants' 1449 form dated 26 October 2005). Oettel et al. teach a method of administering GnRH in combination with an estrogenic compound which is a chemically modified derivative of estradiol or estriol, for example, 14.alpha.,15.alpha.-methylene-1,3,5(10),8-tetraene-3,17.alpha.-diol, in order to treat the side effects associated with GnRH therapy (hot flashes—see claim 7; paragraphs [0006], [0011], [0020]-[0041]). Note that claim 9 recites only that the estrogenic composition be "capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density **or** the hot flashes in the alternative, so although the estrogenic composition taught by Oettel et al. does not change bone mineral density (see paragraph [0071], hot flashes were treated, thus Oettel meets the limitations of claim 9. The suggested regimen in humans is injected Decapeptyl-Depot in a dose of 3.2 mg of triptorelin

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intramuscularly at intervals of four weeks and 1 to 2 mg of 14.alpha.,15.alpha.-methylene-1,3,- 5(10),8-tetraene-3,17.alpha.-diol given in suppository form (see paragraph 55), thus meeting the limitation of claims 9, 12, 13 and 17. Note that a discussion of suitable GnRH antagonists and agonists is found at paragraph [0019] of the instant specification and Decapeptyl-Depot is discussed therein, thus using the specification as a lexicon, the triptorelin taught by Oettel et al. would not be different from the triptorelin recited in the instant claims and would therefore have the same characteristics as recited in claim 9, namely, "a sustained release formulation of a gonadotropin hormone releasing hormone (GnRH) composition capable of releasing the (GnRH) composition for a period of at least about one month at a rate sufficient to induce and maintain chemical castration of the patient". The clinical study reported by Oettel et al. was performed in females, but they also conducted a study of the effects of 14.alpha.,15.alpha.-methylene-1,3,- 5(10),8-tetraene-3,17.alpha.-diol in male rats at a dose equivalent to 0.04mg/kg body weight administered subcutaneously over a 21 day period. Furthermore, the regimen of triptorelin combined with modified estradiol or estriol is suggested for males suffering from prostate cancer (paragraph [0006]), thus does not teach against the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 11, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oettel et al. as applied to claims 9, 12, 13 and 17 above, and further in view of Orsolini (U.S. Patent No. 5,134,122, issued 28 July 1992—on Applicants 1449 form dated 26 October 2005—hereafter the '122 patent), Pike et al. (WO9426207, published 24 November 1994—one Applicants' 1449 form dated 26 October 2005), Cameron et al. (U.S. Patent No. 5,552,412, issued 3 September 1996—hereafter the '412 patent), and as further evidenced by Khosla et al. (J Clin Endocrinol Metab. 2001;

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86: 3555-61). The first issue that must be resolved when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. The teachings of Oettel et al. and how they meet the limitations of claims 9, 12, 13 and 17 are discussed above (see Rejection under 35 U.S.C. 102(b)) and are hereby incorporated. Briefly, Oettel et al. teach a method of administering GnRH in combination with an estrogenic compound which is a chemically modified derivative of estradiol or estriol in order to treat the side effects associated with GnRH therapy (hot flashes—see claim 7; paragraphs [0006], [0011], [0020]-[0041]). The second issue that must be resolved is to ascertain the differences between the prior art and the claims. Oettel et al. do not teach a sustained release formulation of an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 mg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase. In addition, Oettel et al. do not suggest that chemically unmodified estradiol is a preferred embodiment of an estrogenic compound.

Regarding delivery vehicles capable of sustained release, the '122 patent is drawn to a method of preparing a pharmaceutical composition which is aimed at providing a prolonged and a controlled release of a medicament which is obtained in the form of microcapsules of a copolymer of lactic and of glycolic acids (see abstract; claims 1-23). Examples 1-6 of the '122 patent (column 4-6, inclusive) teach how to make

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specific embodiments of the claimed medicaments, which are sustained release compositions of triptorelin and other GnRH agonists and/or antagonists, and the composition taught in Example 1 of the '122 patent is identical to the sustained release formulation of GnRH composition that is recited in the claims. In addition, Pike et al. teach pharmaceutical agents comprising GnRH **and** estrogenic compositions formulated for sustained release (see claims 1-7). In addition, Pike et al. discuss throughout their disclosure various delivery vehicles including a copolymer of lactic and of glycolic acids (polylactide coglycolide—for instance, see p. 11, lines 28-32). See for instance, p. 11, lines 13-24, which addresses the high level of skill and knowledge in the art about delivery vehicle design:

The carrier vehicle for each component is selected from a wide variety of materials which are already known...

In particular, the carrier vehicle of the delivery system is selected such that near zero-order release of the components of the regimen is achieved...A targeted steady-state release can be obtained by suitable adjustment of the design or composition of the delivery system.

See also p. 11, lines 28-33 through p. 12, lines 1-7, which addresses the advantages of the microcapsules:

One suitable formulation to achieve the desired near zero-order release of the components comprises injectable microcapsules or microspheres prepared from a biodegradable polymer such as poly(dl-lactide), poly(dl-lactide-co-glycolide). Polycaprolactone, polyglycolide, polylactic acid-co-glycolide, poly(hydroxybutyric acid), a polyortho-ester or a polyacetal. Injectable systems comprising microcapsules or microspheres of a diameter on the order of about 50 to about 500 m offer advantages over other delivery systems. For example, they generally use less hormone and may be administered by paramedical personnel. Moreover, such systems are inherently flexible in the design of the duration and rate of separate drug release by selection of microcapsule or microsphere size, drug loading and dosage administered. In addition,

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such microcapsules or microspheres can be successfully sterilized with gamma irradiation.

See also p. 12, lines 8-32, which addresses the high level of skill in the state of the art with regard to preparation of microcapsules for steroids (i.e., estrogen) along with suitable references. Taken together, the teachings of the '122 patent and Pike et al. demonstrate that compounds comprising GnRH and estrogenic compositions designed for slow release were known in the art and the person of ordinary skill in the art would know how to design them.

The '412 patent teaches at column 2, lines 40-47 that estrogenic compounds are effective in the treatment of certain prostate cancers and it defines prostatic disease as benign prostatic hyperplasia or prostatic carcinoma (column 8, lines 9-10). The remedies for prostatic diseases taught by the '412 patent is administration of an estrogenic compound, for instance, raloxifene, which may be administered to animals including humans orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, suspensions, etc. (see column 8, lines 23-64), thus the '412 patent teaches the same patient population (those with prostate cancer) and therapeutic components (GnRH and estrogen) and suggests microcapsules as a method of delivery (see column 8, line 23-30, specifically). In addition, the '412 patent teaches that the preferred amount of the active ingredient in the medical composition comprising an estrogenic composition is 0.25 mg to 25 mg in per unit dosage in human patients, which falls within the same dosage recited in claims 10 and 11 (see column 8, lines 59-65). The '412 patent discloses working

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examples showing the salutary effect of estradiol on prostate weight (column 16, lines 47-50) and discloses its importance in maintaining bone mineral density (see column 1, lines 65-66 through column 2, line 1). Although the '412 patent does not discuss how to make the microcapsules, the '122 patent and Pike et al. provide ample guidance on how to design microcapsules and the '412 patent provides guidance to one of skill in the art about dosage of estrogen.

Furthermore, there is also a discussion at column 8, lines 11-22 of the '412 patent that the level of ordinary skill in the art is high and the methods of making the estrogenic compositions discussed therein would be known to chemists of ordinary skill. In short, the combined teachings of the '122 patent, Pike et al. and the '412 patent demonstrate that compounds comprising GnRH and estrogenic compositions designed for slow release were known in the art and the person of ordinary skill in the art would know how to design them and furthermore, provide guidance as to the dosage of estrogenic compound.

Instant claim 16 requires that the level of estradiol released is at a rate between about 25 and 50 $\mu\text{g/day}$, as opposed to instant claims 10 and 11, which recite the release of the estrogenic composition being at a rate of about 10 and 100 mg of estradiol equivalent/day. Nevertheless this amount does not represent an unusually low level. According to Khosla et al. at p. 3560, Figure 2, it was known in the art that levels of estrogen below 40pmol/liter (11pg/ml) may be cause of bone loss in men, which demonstrates that the level below which bone loss occurs in men was well known in the art, and furthermore that the level

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required to prevent bone loss was low. Furthermore, see p. 10, lines 3-9 of Pike et al.:

Typical dose ranges for estrogenic compositions depend not only upon the choice of composition, but also the characteristics of the patient. For an adult human female patient administered estradiol, typical dose ranges are such that the serum level of estradiol is maintained at a level of about 25 to about 140 pg/ml. Most preferably, the serum level of estradiol is about 30 to about 50 pg/ml.

Although Pike et al. are teaching the levels of estradiol that should be obtained in females, this passage demonstrates that 1) there was a recognition that dose ranges of estradiol should be low and that suggests 2) arriving at the correct dose would not require undue experimentation for one of ordinary skill in the art and 3) the preferred embodiment for serum level of estradiol for women (30-50 pg/ml) is not very different than the range of doses for men (shown in Khosla et al., p. 3560, Figure 2) and fall within the range recited in claim 16. In short, the combined teachings of Khosla et al. and Pike et al. teach that ideal dosage of estrogen to stave off bone loss in men was known and Pike et al. suggests that dose ranges depend on choice of composition as well as individual patients, which suggests that dosage of estrogen is understood by one of skill in the art and that optimizing this dosage would not require undue experimentation. One of skill in the art would know where to look for guidance regarding estrogen dose.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Oettel et al. by designing a microcapsule delivery vehicle for the estrogenic composition or estradiol that delivers a sustained release of estradiol or estradiol equivalent at a rate between about 10 and 100 mg per

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day (claims 10 and 11) or alternatively, a rate between about 25 and 50 $\mu\text{g/day}$, as taught in the combined teachings of the '412 patent (which teaches a unit dosage of 0.25 – 25 mg/day), the '122 patent (which teaches how to make microcapsules of a copolymer of lactic and of glycolic acids), Pike et al. (who provide further evidence that the manufacture of microcapsules of a copolymer of lactic and of glycolic acids was well known in the art) and Khosla et al. who provide evidence the levels of serum estradiol below which bone loss occurs in men was well known in the art) for several reasons. First, Oettel et al. provide evidence that men undergoing estrogen therapy could experience cardiovascular complications (paragraph [0018]) and presented a solution in the form of estrogenic compounds that do not carry the side-effects of estrogen. However, the solution proposed by Oettel et al. does not address bone loss and in their clinical trials, bone density was unchanged. Khosla et al. teach the levels of serum estradiol below which bone loss occurs in men. Both the '412 patent and Pike et al. report the salutary effects of estradiol on bone mineral density. The disclosures of the '122 patent and Pike et al. each highlight how to make the microcapsules containing a copolymer of lactic and of glycolic acids which allows for the slow release of pharmaceutical compounds such as GnRH (taught in the '122 patent) and estradiol (taught by Pike et al.). The person of ordinary skill in the art would have been motivated to make a slow or sustained release estrogenic composition as taught by the '122 patent and by Pike et al. because 1) the importance of maintaining a level of serum estradiol that does not result in unwanted side effects was clearly recognized by Oettel et al., Pike et al. and disclosed in the '412 patent and 2) the estrogenic compounds

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taught by Oettel et al. did not improve bone mineral density whereas estradiol does.

With regard to maintaining a release rate of estradiol between about 25 and 50 $\mu\text{g/day}$, optimizing a dosage of estradiol would not require undue experimentation. Ideal dosages of various estrogenic compounds are known to one skilled in the art and this is particularly the case since the estrogenic compounds in the instant claims are limited by a particular use that was known in the art, namely the amelioration of side effects incurred by GnRH therapy. Furthermore, the person of ordinary skill in the art could have reasonably expected success because administration of compounds comprising GnRH and estrogen compositions was well known and established in the art. The final factor to consider when making a rejection under 103(a) is objective evidence in the application indicating obviousness or nonobviousness. In the instant case, the dosage ranges of release of estradiol or estradiol equivalent from the estrogenic composition recited in the claims varies from the mg to μg levels, in other words, one-thousand fold differences, which suggests the same findings as indicated by the prior art, namely, optimization of dosage is well understood by one of skill in the art. Thus the claims do not contribute anything non-obvious over the prior art.

Conclusion

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Bridget E Bunner/
Primary Examiner, Art Unit 1647